Scientific

For this Phase 1 trial, we propose to evaluate the safety of direct muscle injection of genes using a recombinant, replication-deficient, adeno-associated viral (AAV) delivery system. One of the four human sarcoglycan genes, α, β, γ, or Δ, will be administered to relevant individuals with sarcoglycan deficient limb girdle muscular dystrophy (LGMD). LGMD is a heterogeneous group of autosomal dominant and recessive conditions characterized by progressive limb-girdle muscle weakness with variable age of onset. Four of the recessively inherited forms of LGMD are caused by deficiencies in transmembrane proteins called sarcoglycans. Absent, deficient, or altered sarcoglycans (α, β, γ, or Δ) have a profound effect on the dystrophin-glycoprotein complex (DGC) resulting in membrane instability.

Preclinical studies have demonstrated that AAV does not elicit an immune response to the transgene product. In the Δ-sarcoglycan deficient hamster and α and γ-sarcoglycan deficient mice reconstitution of sarcoglycan expression has been demonstrated in skeletal muscle using an AAV vector. The primary objective of this trial is to determine a safe dose of AAV vector delivered via needle injection to a muscle, extensor digitorum brevis (EDB), to be used in subsequent trials of efficacy for LGMD patients with one of the sarcoglycan deficiencies (α, β, γ, or Δ). The primary endpoint on which safety will be assessed is the development of any Grade III or higher treatment-related toxicities. This will be a blinded administration with vector delivered to one foot and saline to the other. The starting dose will be 1.0×10^{11} particles for cohort 1 and 1.0×10^{12} particles for cohort 2. With each cohort, any one of the four AAV-sarcoglycan vectors (α, β, γ, or Δ) could be used at the same concentration. Both toxicity and gene transfer will be assessed for each patient within each cohort by taking a biopsy of the EDB after 43 days. Muscle will be analyzed for: standard histology; immunohistochemistry for expression of the α, β, γ, or Δ sarcoglycan and dystrophin proteins; in situ analyses for mRNA expression; and PCR analyses for the specific transgenes. Immune responses to the vector and sarcoglycan proteins will also be analyzed for neutralizing antibody and lymphoproliferative responses. A standard three-six dose escalation scheme will be used, based on toxicity parameters, to establish the maximum tolerated dose.